Quelles indications et quelles modalités d'organisation pour un prélèvement de moelle en cas de collecte insuffisante de CSP allogéniques ?

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CAS CLINIQUE:

MME. J. D…, 27 ANS, DONNEUSE ALLOGÉNIQUE POUR SON PÈRE

A propos d’un cas clinique

Consultation pré-don:

27 ans, électricienne, pas de tabac ni alcool, pas de toxiques, pas de grossesse, ATCD=0, 1m65, 62 kg

Consentement: signé, TGI ok

Bilan pré don:

biologie normale, bilan séro OK, NFS: GB 5,3 G/L, Hb 140 g/L, plt 258 G/L, ABO compatible

Aptitude finale au don: confirmée

Mobilisation: Granocyte 34, 2 flacons/j pour 4j, à démarrer le 12/02

Cyta: programmée le 16/02

A J0: 27,000GB et 11 CD34/microl

Cyta 1: 0,6x10e6 CD34/kg du receveur (3 MS, différence de poids de + de 50kg)

Que faire?

Procédure JACIE: si greffon obtenu ou prévisible<1,5x10e6 CD34+/kg: PMO

Consult anesthésie le 16/02: OK

PMO: le 18/02 sous AG:

Collecte: 0,8x10e6 CD34/kg

Total: 1,4x10e6 CD34/kg, patient sorti d’aplasie J+30

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Questions et définitions

Poor mobilizers?
défini sur la collecte totale ? La 1ére cyta?
Définis sur le nombre de CD34/microL après mobilisation?
>94% succès de collecte (>2x10e6/kg) si CD34>20/microL
(Guthenson et al, Transfusion 2010, 50(3): 656-662)
Autres définitions?

Stratégies?
PMO?
Continuer cyta?
Autres agents de mobilisation?

Peut on anticiper l'échec de collecte?

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Facteurs prédictifs de mobilisation?

TABLE 2. Effect of the considered variables on the odds of achieving a good mobilization

Variable	OR	SE	p value	95% CI
Male sex	2.51	0.64	0.0005	1.52-4.15
Age*	0.97	0.01	0.007	0.96-0.99
WBC count†	1.19	0.10	0.030	1.02-1.40
G-CSF dose‡	1.34	0.10	0.0005	1.15-1.56

* 1-year increase.
† 1 × 10^9/L increase.
‡ 1 µg/kg increase.

TABLE 3. Results of multivariate analysis of use of lenograstim versus filgrastim as growth factor in addition to the four variables age, sex, WBC count, and G-CSF dose

Variable	OR	SE	p value	95% CI
Male sex	2.49	0.64	0.0005	1.50-4.15
Age*	0.97	0.01	0.005	0.95-0.99
WBC count†	1.21	0.10	0.019	1.03-1.43
G-CSF dose‡	1.34	0.11	0.0005	1.15-1.56
G-CSF type (lenograstim)	2.38	0.69	0.002	1.36-4.19

* 1-year increase.
† 1 × 10^9/L increase.
‡ 1 µg/kg increase.

Facteurs prédictifs positifs:

- High pre GCSF WBC
- younger age,
- male donors
- dose mcg/kg
- Type GCSF

360 donneurs, deux centres italiens, période 1995-2012

Five variables (sex, age, WBC count, and G-CSF form and dose) model:

— Female donors and use of filgrastim: CD34 = 2.95 × WBCs (×10^9/L) + 5.29 × G-CSF dose (µg/kg) – 0.58 × age (years) + 9.32.

— Male donors and use of filgrastim: CD34 = 2.95 × WBCs (×10^9/L) + 5.29 × G-CSF dose (µg/kg) – 0.58 × age (years) + 9.32 + 11.95.

— Female donors and use of lenograstim: CD34 = 2.95 × WBCs (×10^9/L) + 5.29 × G-CSF dose (µg/kg) – 0.58 × age (years) + 9.32 + 7.46.

— Male donors and use of lenograstim: CD34 = 2.95 × WBCs (×10^9/L) + 5.29 × G-CSF dose (µg/kg) – 0.58 × age (years) + 9.32 + 11.95 + 7.46.

BERTANI ET AL.

TRANSFUSION 2014;54:2028-2033.

Facteurs prédictifs de mobilisation (2)?

Table V. Multivariate analysis of factors influencing progenitor cell yields.

	All donors (P-value)	Male donors (P-value)
CD34^{+} cell yield		
Sex	NS	N/A
Age	0·034	0·037
Weight (kg)	<0·0001	0·015
Type of G-CSF	NS	NS
GM-CFC yield		
Sex	NS	N/A
Age	NS	NS
Weight (kg)	NS	NS
Type of G-CSF	0·01	0·004

Yields measured as cells collected/l of blood processed. NS, not sig-

Facteurs prédictifs positifs:

- ➢ Age (<55?)
- ➢ poids (>78kg?)
- ➢ CD34 à mi cyta?

400 donneurs consécutifs, une institution, période 1996-2005

S.J. Ings *et al*

British Journal of Haematology, **134**, 517–525

Table II. Peripheral blood stem cell CD34^{+} cell doses $\times 10^6$/kg, donor characteristics and action taken following eight poor donations.

No.	Recipient CD34^{+} dose	Donor CD34^{+} dose	Total CD34 $\times 10^6$	Age	Weight (kg)	Sex	Related/ unrelated	Action taken
1	0·4	0·7	50·9	52	79	M	R	Transplanted with autologous back-up PBSC
2	0·9	0·7	44·6	27	60	M	R	No further cell collection, 'Top up' for prior transplant
3	1·2	1·5	99·9	45	67	M	R	BM harvest, CD34 = 1·0 $\times 10^6$/kg (7 d post-PBSC)
4	1·5	1·6	88·7	52	54	F	U	BM harvest, CD34 = 1·1 $\times 10^6$/kg (3 d post-PBSC)
5	1·6	1·7	136·0	23	80	M	R	No further cell collection
6	1·6	1·8	175·4	58	95	F	R	No further cell collection
7	1·7	1·9	136·0	45	71	M	U	Accepted by recipient transplant centre.
8	1·9	2·2	133·4	56	62	F	R	No further cell collection

Facteurs prédictifs de mobilisation (3)?

Facteurs prédictifs positifs:
- Baseline value CD34 >1/microL?

128 donneurs en prospectif, une institution, période 2012-2015

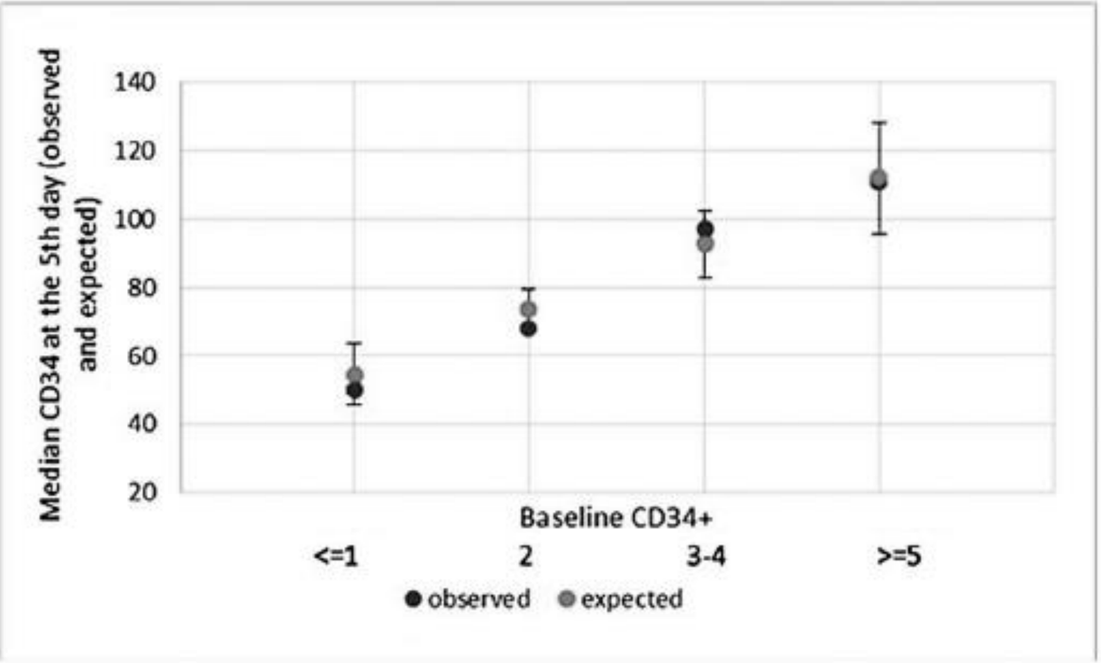

Figure 2. Scatter plot of observed and predicted median values of CD34+ on day 5 (with 95% confidence interval on model data) on baseline CD34+ model adjusted by age gender and blood volume (CD34+ cell counts/µL).

M. Martino et al. / Biol Blood Marrow Transplant 23 (2017) 1215–1220

Facteurs prédictifs de mobilisation: Review, 2013

Table 2. Impact of demographic data and hematological parameters on mobilization efficacy in healthy allogeneic PBSC donors (after Hölig and Kroschinsky, with modifications)

Author	Donors, n	Sibling/unrelated	Age, median, (range), years	G-CSF preparation, daily dose	Factors affecting mobilization of CD34+ cells and apheresis yield
De la Rubia et al., 2002 [29]	261	sibling and unrelated	38 (2–72)	filgrastim lenograstim 10 µg/kg	positive influence: divided G-CSF dose, WBC on day 5 of G-CSF negative impact: female gender, age > 38 years no influence: baseline CBC, G-CSF preparation, G-CSF dose
Suzuya et al., 2005 [30]	59	sibling	16 (3–63)	lenograstim filgrastim nartograstim 10 µg/kg	positive influence: WBC, platelet count at baseline negative impact: BMI, age no influence: G-CSF preparation, sex
Ings et al., 2006 [24]	400	263 siblings 137 unrelated	41 (12–74) 37 (20–59)	filgrastim lenograstim 10 µg/kg	positive influence: weight > 78 kg, male sex (only apheresis yield, not peripheral CD34 count) negative impact: age > 55 years no influence: G-CSF preparation
Vasu et al., 2008 [31]	639	sibling	40 ± 13	filgrastim 10–16 µg/kg/day	positive influence: weight, G-CSF dose, baseline platelet count, prior apheresis for DLI collection negative impact: age, female gender, white ethnicity
De Lavallade et al., 2009 [32]	129	sibling	51 (19–70)	filgrastim median 8.9 µg/kg	positive influence: weight, G-CSF dose no influence: age
Richa et al., 2009 [33]	195	sibling	52 (17–71)	filgrastim 10 µg/kg	negative influence: age no influence: sex, weight and comorbidities
Al-Ali et al., 2011 [34]	167	sibling	47 (18–74)	filgrastim 2 × 5 µg/kg	negative influence: age (donors > 50 years mobilized less well) no statement regarding other variables
Hölig et al., 2013 [80]	4,393	465 sibling 3,928 unrelated	48 (2–73) 34 (18–61)	lenograstim 7.5 µg/kg	positive influence: BMI, baseline platelet count, male sex, divided G-CSF dose negative impact: female sex, smoking, alcohol consumption, age (in sibling donors only)

WBC = White blood cell count; CBC = complete blood count; BMI = body mass index; DLI = donor lymphocyte infusion.

G-CSF in Healthy Allogeneic Stem Cell Donors Transfus Med Hemother 2013;40:225–235

Facteurs positifs prédictifs communs:
- Male sex? BMI/weight? *Age*? WBC/plt?
- Divided Dose? *Lenograstim*?

Holig et al, **4393 donors** (90% MUD) Dresden

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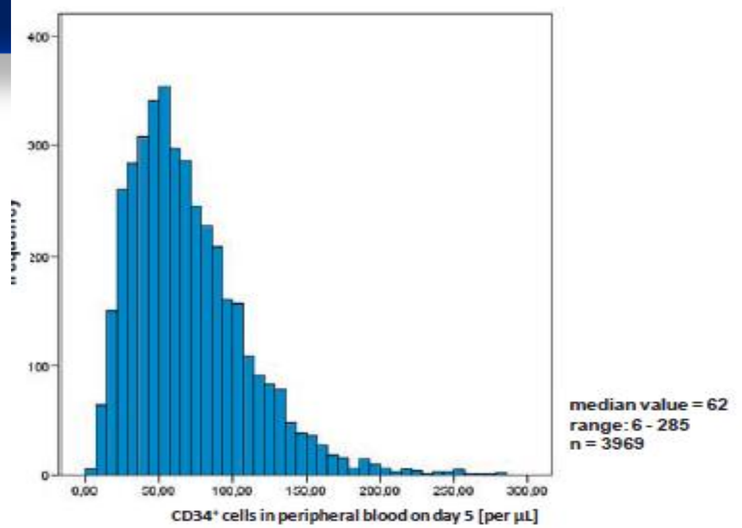
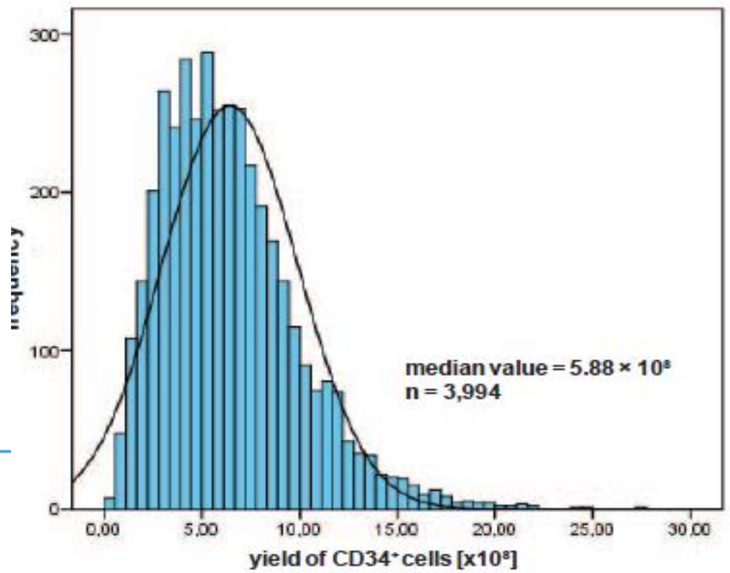
Facteurs prédictifs de mobilisation: Review (2)?

Variabilité inter individuelle pour un même protocole de mobilisation**:**
Lenograstim 7,5 microG/kg
N=3928 MUD
Poor mobilizers: 2% (RD), 0,45% (MUD)
Polymorphisme CXCL123'-A, VCAM-1, CD44?

G-CSF in Healthy Allogeneic Stem Cell Donors Transfus Med Hemother 2013;40:225–235



ig. 1. Concentration of CD34+ cells in peripheral blood on day 5 of G-'SF-application, prior to the first leukapheresis (counts per µl).



ig. 2. Yield of CD34+ cells in the first leukapheresis (×10⁸).

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Recommandations internationales: GITMO/SIDEM

Question 1: Which is the best schedule of myeloid growth factors in PBPC mobilization?

RECOMMENDATIONS. *Filgrastim and lenograstim are the growth factors of choice for mobilizing PBPCs in healthy donors. The recommended dose is 10 µg/kg/body weight daily, preferably by a split administration, until the target dose has been collected, for a maximum of 5 days, provided that white blood cell (WBC) count does not exceed 60×10^9/L.*

A dedicated policy should be applied to donors under the age of 18 years and in the haploidentical setting. Poor mobilizer sibling donors should be proposed additional procedures, such as a prolonged stimulation and collection not longer than 7 days, or marrow stem cell collection.

No evidence definitely supports safety and efficacy of G-CSF biosimilars for PBPC mobilization in the allogeneic SCT setting (adults and children).

PIERELLI ET AL.

PBPC MOBILIZATION AND COLLECTION

Volume 52, April 2012 **TRANSFUSION**

Consensus conference

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EN PRATIQUE?

Prélèvement de moelle

Les points clés: **procédure commune souhaitable avec le bloc/équipe d'anesthésie**

- **Information donneur** :

✓ indispensable en amont: standard JACIE (risque de refus si info non donnée ou comprise)

- **En urgence?** :

✓ le patient est conditionné: le plus tôt possible
✓ récupération plaquettaire post cyta recommandée: dans les 48-72h?
✓ Tenir compte de la désérythrocytation éventuelle+++

- **Consultation AG** : systématique? Selon possibilités de chaque centre

- **Collecte?** : préleveur expérimenté…

- **Suivi donneur** :

✓ clinique standard (fer per os, NFS de contrôle…)
✓ suivi psychologique recommandé+++
✓ Ateliers SFGM-TC 2018 pour donneurs apparentés,
✓ A Billen et al, BMT 2014: A review of the haematopoietic stem cell donation experience

JACIE?

- **Standards JACIE Donneurs allo:**

B6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

B6.2.1.4 Alternative collection methods.

B6.2.5 The donor shall have the right to refuse to donate or withdraw consent.

B6.2.5.1 The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal in the event that consent is withdrawn after the recipient begins the preparative regimen.

B6.3.2.2 Mobilization for collection of HPC, Apheresis.

Explanation:
Mobilization requires that evaluation occur for any medical condition that would expose the donor to the risk for thrombotic events. This evaluation must be documented, including the pre-collection and collection time frames specific to growth factor administration.

If the donor is at risk of failure to mobilize, the Clinical Program must also evaluate the donor for fitness to undergo a marrow collection if necessary, and inform the donor, to protect the recipient who has already begun the preparative regimen.

Table 4. Factors influencing psychological outcomes

Death of the recipient/worse outcome in recipient	Unrelated donors: Grief was often surprisingly intense, given the fact that the recipient was a stranger, feelings of guilt were rare.[69] Related donors: Associated with a more stressful experience.[66] Recipient deterioration may significantly adversely impact donor psychosocial status.[89] Significantly higher Beck depression scores 6 months following donation.[70] Donors felt less as if their donation had really helped their sibling as time passed. However, bereaved donors experienced global psychological gains including enhanced self-esteem, happiness and life-satisfaction compared with donors whose siblings were still living.[90]
More physical difficulty with donation	Associated with feeling less positive psychologically about the donation.[49] BM donation was associated with more physical morbidity and negative effects on QOL up to 1 month after donation than was PBSC donation (BM vs PBSC).[25] BM donors mood scores were worse 1 week after compared with before donation, whereas PBSC scores did not change (BM vs PBSC).[25] More likely to experience donation as stressful.[65,66]
Longer collection times/large volumes collected	Less positive psychological outcomes.[65] Less willing to donate again in future.[65]
Ambivalence	Greater ambivalence associated with more physical and psychological difficulties with donation.[49] Factors associated with higher ambivalence: higher education, donors who were discouraged by others,[49] exchange motives (weighing costs and benefits), idealized helping motives,[72] extrinsic pressure,[71] some ethnicities (Asian Americans)[73] Factors associated with lower ambivalence: more frequent blood donors, happier individuals, those who believed the patient's chances of survival were better,[49] empathy motives,[72] intrinsic commitment.[71]
Related vs unrelated	Depression scores significantly higher in related donors, before and after donation.[43]
Family dynamics and emotional support	More positive experience if better emotional support from family, friends and hospital staff.[66,74] Married donors had fewer negative psychological reactions shortly following donation.[49]
Preparation for donation	Adequacy of preparation for donation influences experience.[74]

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A review of the haematopoietic stem cell donation experience, A Billen et al, BMT 2014

Poursuite cytaphérèses

Questions non résolues:

- **Autres facteurs de croissance/mobilisation**:
  - ➢ pas d'AMM donneur sain pour le plerixafor, quelques études pilotes (Ciceri et al, 2015, n=10; Locatelli et al, 2014, n=30, Devine et al, 2008 n=24)

- **Augmentation de la dose de GCSF**: pas de données…

- **Faisabilité** : au cas par cas, risque thrombopénie…

- **Seuil minimum de CD34 à collecter**:
  - ➢ 2x10e6/kg receveur? Généralement admis pour risque de non prise

- **Suivi donneur** : suivi psychologique recommandé+++

- **2e cycle de mobilisation**?
  - ➢ Résultats attendus identiques, risque anomalies NFS prolongées
  - ➢ WMDA guidelines, Confer DL et al, BMT 2011

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Conclusions

- Pas de facteur prédictif fiable identifié dans la littérature: âge, sexe, poids/BMI, WBC/plt pré GCSF…

- 2 à 5% de mauvais mobilisateurs: polymorphisme génétique? (GCSFR, VCAM, SDF-1…)
  - ➢ Donc choix du donneur : jeune, homme, pas d'ATCD, poids?
  - ➢ et adapter la dose de GCSF au plus près de 10mcg/kg

- Information et suivi du donneur: importance majeure car situation toujours difficile

- PMO à organiser en urgence si possible car patient conditionné,
  - ➢ sécurité du donneur à assurer (consultation AG, thrombopénie, PEC psycho, contrôle NFS…)
  - ➢ Procédure commune bloc/anesthésie/équipe prélèvement

- Poursuite de la cyta à discuter au cas par cas, inutile si CD34<5/microL
  - ➢ Pas d'AMM pour donneur sain du plerixafor: recherche clinique